UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,849	11/13/2003	Charles M. Zepp	SEPR-P01-056	9511

28120 7590 09/10/2007

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
09/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,849	ZEPP ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *3-10,12,19,22 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,11,13-18,20,21 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' election **without traverse** of Group Ib with 2-thiouracil as the elected species in the reply filed on 6/28/07 is acknowledged. This election reads on Claims 1, 2, 11, 13-18, 20, 21, and 23-29. The Restriction Requirement is thus deemed to be proper and is made **Final**.

2. Claims 3-10, 12, 19, 22, and 30 are withdrawn, 37 CFR 1.142(b), from consideration because they are contained in non-elected groups.

3. . Claims 1, 2, 11, 13-18, 20, 21, and 23-29 are under consideration.

Drawings

4. The drawings are objected to because they are difficult to read. For example, the x-axis labels are too small and of poor text quality. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each

drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

5. The Specification is objected to because the reference to, and brief description of the drawings, as set forth in 37 CFR 1.74, are inadequate. A more detailed description of is required and should include a description for **each** figure, including a description of **each frame** of the figures.

Appropriate correction is required.

It is noted that the data, as presented, have no indications of statistical significance.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 11, 13-18, 20, 21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims

contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claim 1 recites compounds of Formula I or "**prodrug or metabolic derivative thereof**". There is insufficient written basis for prodrugs or metabolic derivatives of compounds of Formula I in the Specification. Claims 1, 11, 18, 21, and 29 recite R-group substituents of Formula I, where **valence and stability permit**. There is insufficient written basis for this limitation of formula I in the Specification.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Elli Liily*, 119 F.3d at 1566 (emphasis added). The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function

and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Elli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant has failed to provide any structural characteristics, chemical formula, name(s) or physical properties of prodrugs or metabolic derivatives of compounds according to Formula I, or R-group substituents of Formula I based upon R-group/Formula I valence and stability, aside from a broad recitation that such are contemplated for use in the invention. As such, it is not apparent that Applicant was actually in possession of, and intended to use within the context of the present invention, any specific compounds so designated.

8. Claims 1, 2, 11, 13-18, 20, 21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method for **reducing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, by administration of 2-thiouracil prior to the cisplatin exposure, does not reasonably provide enablement for **preventing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, or **preventing or reducing** hearing impairment caused by other chemical agents (*i.e.*, aminoglycoside antibiotics, ototoxic diuretics, or certain quinine-like compounds)), noise, or aging . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

The instant claims are drawn to a method of "preventing, reducing, or otherwise treating hearing impairment due to noise-induced hearing loss (NIHL), aging, or chemical-induced hearing loss (CIHL), comprising administering to a subject a compound" having a structure according to Formula I of Claim 1, between 72 hrs before and 36 hours after exposure to the hearing-impairing agent.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method of "preventing, reducing, or otherwise treating hearing impairment due to noise-induced hearing loss (NIHL), aging, or chemical-induced hearing loss (CIHL), comprising administering to a subject a compound" having a structure according to Formula I of Claim 1. The CIHL causing agent is an ototoxic chemotherapeutic drug selected from aminoglycoside antibiotics, platinum-containing

antineoplastic agents, certain quinine-like compounds, or ototoxic diuretics. The therapeutic agent may be administered between 72 hours before to 36 hours after exposure to the agent causing the hearing loss.

Merriam-Webster's Online Dictionary defines the term "prevent" as "to keep from happening or existing, to deprive of power or hope of acting or succeeding ". The interpretation of the instant claims allows for the complete cure and eradication or total elimination of hearing loss caused by noise, chemicals or aging by the administration of the compounds defined by Formula I. Additionally, the claims' recitation of preventing or treating hearing loss caused by age defines a population of everyone with treatment spanning his or her entire life.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The Merck Manual teaches that age-related hearing loss is not preventable and most other causes of hearing loss are irreversible (*see* page 6, "Prevention and Treatment", 1st and last paragraphs). For example, Goran *et al.* (U.S. Publication No. 2002/0180388) teach that cisplatin-induced hearing loss is non-reversible (*see* paragraph 53, lines 10-12).

Thus, it is not understood how one skilled in the art can reasonably expect that the instant compounds can be administered in order to have the "preventive" effect.

(5) The relative skill of those in the art:

The relative skill of those in the art of pharmacology and medicine and the unpredictability of the pharmacological and /biological arts are very high. In fact, the courts have made a distinction between mechanical elements, which function the same

in different circumstances, yielding predictable results, and chemical and biological compounds, which often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. Likewise, the physiological or pharmaceutical activity of treating or preventing retinopathy, particularly retinopathy of undefined etiology, is an unpredictable art.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The Specification has provided guidance and a working example for a method of **reducing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, by administration of 2-thiouracil **prior** to the cisplatin exposure. The Specification provides *in vivo* data demonstrating a reduction of hearing loss in rats treated with 2-thiouracil prior to administration of cisplatin. The presentation of the data in the provided figures makes it is impossible to determine whether any of the other treatments displayed in the figures had any significant protective effects.

However, the Specification does not provide guidance or a working example for a method of **preventing** hearing impairment caused by the platinum-containing antineoplastic agent, cisplatin, or **preventing or reducing** hearing impairment caused by other chemical agents (*i.e.*, aminoglycoside antibiotics, ototoxic diuretics, or certain quinine-like compounds)), noise, or aging. There is no guidance or working example for

preventing or reducing hearing impairment when treatment is given **after** patient exposure to the causative agent. The most extreme example of the deficiencies of the claims is that of the method of preventing or reducing hearing impairment caused by aging. The Merck Manual teaches that age-related hearing loss affects everyone and begins some time after the age of 20 (*see* "Age", pages 1-2). Therefore, since age-related hearing loss is irreversible (*supra*), the administration of the claimed compounds would need to begin before any loss occurs and must continue indefinitely. Since most chemical agents have potentially deleterious effects, lifetime treatment with such a compound, particularly one that has not been demonstrated to be beneficial for the treatment of age-related hearing loss, would inadvisable.

Although the Applicants may serve as their own lexicographer, the definition of "prevents" recited by the Applicants in the Specification (page 5, lines 16-19), is repugnant to one skilled in the art and is therefore not acceptable.

(8) The quantity of experimentation necessary:

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. *In re Fisher*, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. *In re Fisher*, 427 F.2d 839, 166 USPQ 24; *Ex Parte Hitzeman*, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires

more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. *In re Wright*, 999 F.2d 1562-63, 27 USPQ2d 1575. The Office maintains a very high standard of enablement for claims drawn to a methods of prevention. As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the claimed methods of prevention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

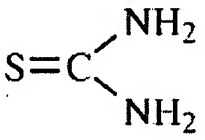
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. The elected specie (2-thiouracil) appears to be free of the prior art, therefore the search has been extended according to current Markush practice.

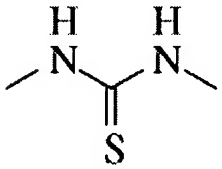
11. Claims 1, 11, 13, 15, 17, 21, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Goran et al (U.S. Patent Publication 2003/0180388, priority date 1/17/2002).

Goran et al. teach the administration of thiourea or dimethylthiourea to reduce chemical induced hearing loss, which includes the chemotherapeutic agent, cisplatin (*see* paragraphs 7-8, page 1). Goran et al. also teach a kit that comprises a chemotherapeutic agent, such as cisplatin, an ototoxicity-preventing agent that is thiourea or dimethylthiourea and instructions for the use and administration of the agents (*see* paragraph 65, page 6). The protective compound is administered directly to the ear by mini-osmotic pump or direct injection into the cochlea or middle ear, or by any other method suitable method for delivery of the therapeutic agent to the inner ear (*see* paragraphs 62 and 63, page 6) prior to administration of the ototoxic substance (cisplatin) (*see* paragraph 70).

Thiourea has the following structure:



Dimethylthiourea has the following structure:



These two compound structures meet the structural requirements of Formula I of the instant application and therefore satisfy the structural requirements of the instant claims.

Therefore, Goran et al. anticipates all the limitations of Claims 1, 11, 13, 15, 17, 21, and 29 of the instant application.

12. Claims 21, 23-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Principles of Pharmacology (Principles of Pharmacology: Basic Concepts & Clinical Applications, 1995).

Principles of Pharmacology teaches the compositions and dosage forms as required by Claim 21. The reference teaches the use of thiourylenes, which include, methimazole (MMI), propylthiouracil (PTU), and carbimazole, to inhibit thyroid hormone synthesis (*see* page 802, last paragraph). The structures of these compounds are presented in Figure 45.5 of the reference (*see* page 803). These structures meet the structural requirements of Formula I of the instant application and therefore satisfy the structural requirements of the instant claims. Principles of Pharmacology teaches oral dose ranges for each of these compounds (*see* page 804, "Preparation and Doses). For example, the dose range for PTU is 300-1200 mg/day. This is equivalent to 4.3-17.1 mg/kg/day for a 70 kg individual.

Therefore, Principles of Pharmacology anticipates all the limitations of Claims 21, 23-28 of the instant application.

Conclusion

13. Claims 1, 2, 11, 13-18, 20, 21, and 23-29 are rejected.

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on Mon-Thur 8:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GP

Phyllis Spivack
8/31/07

PHYLLIS SPIVACK
PRIMARY EXAMINER